Short Course on Heterocyclic Chemistry

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Lecture 1. Introduction to Heterocyclic Chemistry. Aromaticity and Tautomerism, and Reactions of Heteroaromatic Rings with Electrophiles.

References at foot of pages are to corresponding sections in "Handbook of Heterocyclic Chemistry" 2nd Edition, 2000, Pergamon/Elsevier by A. R. Katritzky and A. F. Pozharski

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I. INTRODUCTION

1. The Rationalization of Reactivity

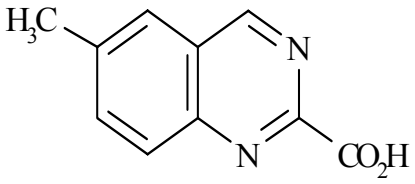
A major objective of the present course of lectures is the rationalization of the reactivity of heteroaromatic compounds. Thus if we look at a compound such as 6-methylquinazoline-2-carboxylic acid we should be able to have a good guess at the reactions that it will undergo by the comparisons shown in Scheme 1. We aim to consider reactivity in such a manner as to facilitate the deduction of the behavior of heterocycles likely to be encountered in real situations.

Scheme 1. Rationalization of Reactivity

A. Aim is to be able to deduce

(i) expected behaviour under given conditions

(ii) conditions required for given behaviour for polyfunctional compounds of moderate complexity, e.g.:



B. Method is to base deductions on simpler compounds of known chemical properties. The above structure is therefore divided into various portions:

(a) CO_2H group	benzoic acid, pyridine-2-carboxylic acid
(b) Methyl group	toluene, 2-methylnaphthalene
(c) Benzenoid ring	benzene, naphthalene, 2-methylnaphthalene
(d) Heterocyclic ring at nitrogen	pyridine, pyrimidine
(e) Heterocyclic ring at carbon	pyridine-2-carboxylic acid

2. Saturated and Partially Saturated Heterocycles

Some of the major differences in the reactivity of these compounds from that of their acyclic analogs are illustrated in Scheme 2. In three- and four-membered rings, ring strain is very important and this significantly increases the reactivity of such compounds compared to the corresponding acyclic derivatives. In five-membered rings, there is no ring strain, and generally reactivity is similar to that of the open-chain analogs; however, steric hindrance at the heteroatom is reduced. Six-membered heterocyclic rings adopt conformations similar to those of their carbocyclic analogs: thus we should find chair forms similar to cyclohexane and half chairs similar to those found in cyclohexene and cyclohexadiene. Importantly, in dihydro derivatives of both five- and six-membered aromatic compounds, there always exists the possibility of aromatization.

Scheme 2. Saturated and Partially Saturated Heterocycles

On the whole very similar to their acyclic analogs. Main differences are:

A. Ring strain in three- or four-membered rings

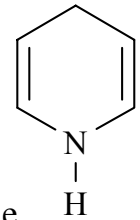
For example  ethylene oxide is much more reactive than acyclic ethers

B. Less hindered particularly in five-membered rings

For example  tetrahydrofuran is more basic and coordinates more readily than acyclic ethers

C. Conformational stability in six-membered rings, e.g. piperidine exists in chair conformation

1,3-cyclohexadiene cyclohexene cyclohexane NH-eq NH-ax

D. Possibility of easy aromatization in dihydro derivatives 

For example dihydropyridine is easily oxidized to pyridine

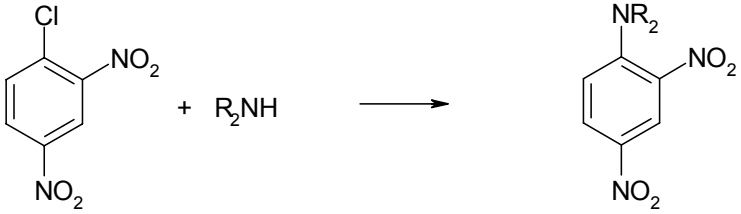
Further information: see Handbook, pp. 238, 246,485.

Further examples of the difference between freely rotating acyclic compounds and their (confomationally restricted) cyclic analogs are given in Scheme 3.

Meldrum's acid is $10^{8.6}$ times more acidic, resulting from the different conformations of the cyclic and acyclic species (alignment of dipoles) and from the greater delocalization of the negative charge in the more planar anion.

Scheme 3. Differences between saturated heterocyclics and analogous acyclics

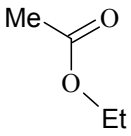
Nucleophilicity



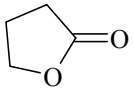
Piperidine is about 100 times more reactive than ethylpropylamine, though their base strengths towards H_3O^+ are very similar.

Polarity: Dipole moments - sensitive to the direction of the constituent dipole (polarity)

ethyl acetate
bp.78 ^{0}C



1.9 D vs

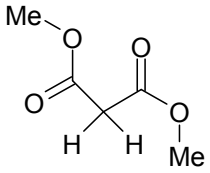


4.1 D

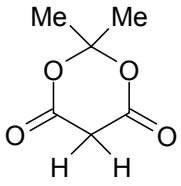
butyrolactone
bp.205 ^{0}C

Acid Strength

dimethyl malonate
pKa ~17 in H_2O



vs



pKa (H_2O)
4.8
(close to acetic acid)

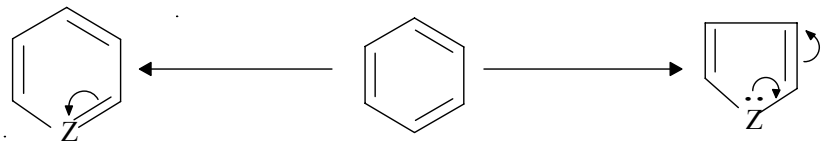
Meldrum's acid

3. Heteroaromatic Compounds as Modified Benzenes

Heteroaromatic compounds with 5- and 6-membered rings are best considered as modified benzenes. There are two quite distinct ways in which benzene can be modified by the substitution of a heteroatom for one or more of the carbon atoms of the ring. It is fundamental that in heteroaromatic compounds two different types of heteroatoms exist: (i) pyridine-like nitrogen atoms (and especially NR^+, O^+, or S^+) are electron withdrawing, (ii) pyrrole-like nitrogen, oxygen and sulfur atoms (and especially N^-) are electron donating. The interrelationship of the various classes of heteroaromatic compounds as regards their derivation from benzene is shown in Scheme 4.

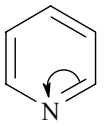
Quaternization of the pyridine nitrogen enhances the electron-attracting properties of the nitrogen and strong electron attraction towards O^+ and S^+ is found in pyrylium and thiopyrylium salts, respectively. The introduction of further pyridine-like nitrogen atoms into either pyridine or pyrrole tends to decrease the reactivity towards electrophiles and increase the reactivity towards nucleophiles.

Scheme 4. Heteroaromatic Compounds as Modified Benzenes
Four Main Classes of Heteroaromatic Compounds

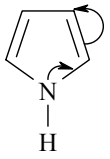


replace CH by
Z = N, NR^+, O^+, or S^+
can be done repeatedly
"π-deficient heterocycles"

replace CH:CH by
Z = O, S, NR or N^-
can be done once only
"π-excessive heterocycles"



C=N: compare with
C=O carbonyl



compare with enamine

Six-Rings
with one hetero atom

Six - Rings
with several hetero atoms

Five - Rings
with one hetero atom

Five - Rings
with several hetero atoms

Aromaticity has major effects on reactivity, stability, and properties. Aromaticity is clearly a quantitative property, i.e. some compounds are more aromatic than others. After much difficulty and controversy, it has recently been shown that while no single scale of aromaticity exists, there are two major effects: one influences geometrical properties and stabilities, and the other magnetic properties. Practical effects of the degree of classical aromaticity on heteroaromatic reactivity are large and important as summarized in Scheme 5. The type of heteroatoms present has a major influence on the stability: pyridine-like nitrogen atoms have the least effect; pyrrole-like nitrogen atoms more; sulfur still more; and oxygen atoms cause the greatest decrease in aromatic stability. The number of heteroatoms influences mainly the magnetic properties.

Scheme 5. Practical Effects of Degree of Classical Aromaticity on Heteroaromatic Reactivity and Structure

A. Tendency to give addition products rather than substitution products increases as aromaticity decreases

B. Cyclic transition state reactions become far more favored as aromaticity decreases

C. Tautomeric structure is greatly influenced by the degree of aromaticity

D. Facility to undergo unimolecular reactions increases as aromaticity decreases

II. REACTIVITY OF HETEROAROMATIC COMPOUNDS

1. Classes of Reactions

In our consideration of the reactions of aromatic compounds, we make a distinction between reactions which take place at the ring and those which take place at a substituent. This separation is possible in most but not all cases. Scheme 6 shows the five fundamentally different ways in which reactions can take place on an aromatic ring. These include reactions with all the different classes of reagents that we have listed and also unimolecular reactions which proceed under the influence of heat or light, but without requiring another reagent. We make subdivisions of reactions with electrophiles mainly between those which proceed at ring nitrogen and those which proceed at ring carbon atom. Similarly, nucleophiles can attack either a ring carbon or at the hydrogen atoms attached to ring carbon.

Scheme 6. Reactivity of Heteroaromatic Compounds

A. Reactions of the Rings and Effect of Substituents on Ring Reactions

1. Reactions which are initiated by the attack of electrophiles
   a. at Nitrogen b. at Carbon

2. Reactions which are initiated by the attack of nucleophiles
   a. at Ring Carbon b. at Ring C-H

3. Reactions which are initiated by attack of free radicals and reactions at surfaces

4. Reactions which are initiated by attack of dienes, dienophiles, 1,3-dipoles or dipolarophiles (cyclic transition state reactions)

5. Unimolecular reactions which proceed spontaneously (with no other molecule) thermally or photochemically
   a. Fragmentations b. Rearrangements c. Ring Opening

B. Effect of the Rings on Reactions of Substituents

1. Substitution on C-atom

2. Substitution on N-atom

2. Influence of Heteroatoms and Reactivity of Heteroaromatics

The nitrogen atom in pyridine is electron-attracting and makes pyridine more reactive at carbon towards nucleophiles than benzene, but less reactive at carbon towards electrophiles than benzene. On the other hand the nitrogen atom in pyrrole is electron donating and this makes pyrrole much more reactive towards electrophiles at carbon than benzene.

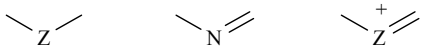
Influences of the heteroatoms on heteroaromatic ring reactivity are set out in Scheme 7. The modification of benzene by introduction of heteroatoms has major effects on the reactivity. As already mentioned, pyridine-like heteroatoms act as electron sinks and withdraw electrons from other ring positions, whereas pyrrole-like heteroatoms act as electron sources and increase the electron density at the other ring atoms. Reduced aromaticity and lower bond energies also have big effects.

Scheme 7. Influence of Hetero Atoms on Heteroaromatic Ring Reactivity

1. Reactions with Electrophiles

at N: 

very reactive reactive unreactive never

at C: 

reactivity increased decreased much decreased

where Z = O, S, NR, and especially N^-

2. Reactions with Nucleophiles

at C: helped by  and especially by 

at CH: helped by  and especially by 

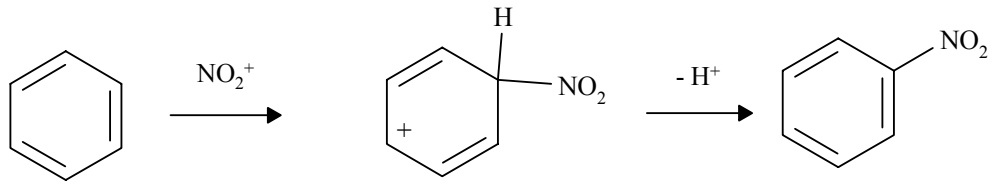
where Z = O, S, or NR

3. Reactions with Free Radical and at Surfaces	less affected by heteroatom substitution
4. Cyclic Transition State Reactions	facilitated by O-hetero atom and by multi hetero substitution (i.e. lower aromaticity)
5. Spontaneous Thermal/Photochemical Reactions	facilitated by multi-heteroatom compounds, especially by N-N

The typical reactions of benzene are those of electrophilic substitution (Scheme 8). For example, in nitration the electrophile NO_2^+ attacks a benzene carbon atom, gives an intermediate, often called a "Wheland intermediate" which then loses a proton to give the final product, nitrobenzene. Other typical electrophilic substitution reactions of benzene with halogenation, sulfonation, and Friedel-Crafts alkylation and acylation. The reaction of benzene with electrophiles is considered to proceed via a π- and a σ-complex.

Scheme 8. Reactions of Benzene with Electrophiles

A. Mechanism of Nitration of Benzene



σ-complex

B. Other Electrophilic Substitution Reactions of Benzene

Halogenation (Cl_2, Br_2), Sulfonation (SO_3)
Friedel-Crafts alkylation ($RCl / AlCl_3$) Friedel-Crafts acylation ($RCOCl / AlCl_3$)

III. ELECTROPHILIC ATTACK AT RING NITROGEN

1. General

An overview of our treatment of electrophilic attack at a ring is shown in Scheme 9.

Scheme 9. Overview of Electrophilic Attack at Ring

Electrophilic Attack at Ring Nitrogen

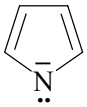
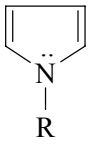
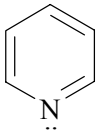
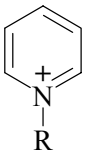
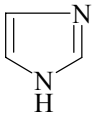
1. General - different types of N-atom, typical products
2. pK_a Values of Nitrogen Heteroaromatics
3. Effect of Substituents on pK_a of Nitrogen Heteroaromatics
4. Steric Effects - Reaction with Lewis Acids and Metal Cations
5. Reactions with Alkyl and Acyl Halides
6. Reactions with Halogens
7. N-Oxidation and N-Amination

Electrophilic Attack at Ring Carbon

1. Ease and Nature of Reaction
2. Five-Membered Rings with one heteroatom: Neutral Species
3. Pyrrole Anions
4. Six-Membered Rings
5. Azoles

More precisely, four distinct types of nitrogen atoms occur in heteroaromatic chemistry: neutral and anionic pyrrole-like nitrogen, and neutral and cationic pyridine-like nitrogen. The tendency of these nitrogen types to react with electrophiles varies widely, as explained in Scheme 10.

Scheme 10. Reactions of Heterocycles with Electrophiles at Nitrogen Atoms

pyrrole anion	pyrrole	pyridine	pyridinium cation	imidazole
				
Reacts very easily with lone pair in ring plane	almost no reactivity (lone pair needed for aromaticity)	reacts fairly readily	no reaction (no lone pair)	nitrogen atoms are different

Notes:

(i) Electron-donor groups in the ring increase the reactivity of the N-atom towards electrophiles

(ii) Electron-acceptor groups decrease the N-atom reactivity towards electrophiles

(iii) Bulky alpha-substiuents can hinder reactions with electrophiles especially in six-membered rings

(iv) In general reactions are easily reversible and resemble those of a tertiary amine

(v) Typically addition reactions with H+, Lewis acids, metal ions, halogens and peracids

Heteroaromatic compounds containing an uncharged pyridine-like nitrogen atom behave as tertiary amines with reactivity towards electrophiles as exemplified in Scheme 11.

By contrast, pyrrole and its analogs do not react easily at the heteroatom with electrophilic reagents. Thus, for example, thiophene does not form readily a sulfoxide or sulfone. However, in the azoles, the pyridine-like nitrogen atoms are basic and nucleophilic. The nucleophilicity of the azoles is highest in imidazole, less in pyrazole and falls further with the introduction of oxygen (especially), sulfur or further nitrogen atoms into the ring.

Di-, tri-azines, etc. react similarly to pyridine with electrophiles at their nitrogen atoms. However, the additional nitrogen atoms mutually reduce their basicity and nucleophilicity.

Scheme 11. Electrophilic Attack at Neutral Pyridine-Like Nitrogen

The lone pair of electrons on the nitrogen atom in pyridine behaves very similarly to that in trimethylamine and other tertiary amines and reacts under mild conditions with electrophilic reagents:

(i) Proton acids give salts

(ii) Lewis acids form coordination compounds

(iii) Transition metal ions undergo complex formation

(iv) Reactive halides give quaternary salts

(v) Halogens form adducts

(vi) Certain oxidizing agents yield amine oxides

(vii) Aminating agents give N-amino derivatives

Further information: see Handbook, p.176.

2. pK_a as a quantitative means of susceptibility to attack by electrophiles

As is next explained, a most useful quantitative indication of the tendency to undergo electrophilic attack at nitrogen in provided by pK_a values. In the whole discussion, we use pK_a values and not pK_b values. The definition of pK_a and pK_b values are shown in Scheme 12. Note the relationship between pK_a and the now no longer used classic pK_b definition.

Scheme 12. pK_a as Universal Measure of Acidity as well as of Basicity

A. Definition of pK_a of Conjugate Acid

$HA \rightleftharpoons H^+ + A^-$

or $HB^+ \rightleftharpoons H^+ + B$

$pK_a = -\log_{10}([H^+][A^-]/[HA])$

B. Definition of pK_b (now obsolete)

$B + H_2O \rightleftharpoons BH^+ + OH^-$

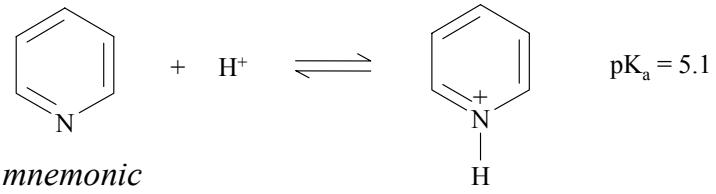
$pK_b = -\log_{10}([BH^+][OH^-]/[B][H_2O])$

now $[H^+][OH^-]/[H_2O] = 10^{-14}$

therefore $pK_a = 14 - pK_b$

C. Example:

We consider the basicity of pyridine in terms of the pK_a of the conjugate acid - the pyridinium cation



D. Useful mnemonic

The pK_a designates that pH where the two species are present at equal concentration

i.e. at pH = 5.1 pyridine is 50% protonated

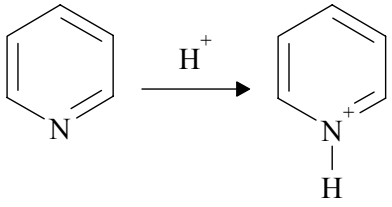
at pH = 6.1 pyridine is 10% protonated

at pH = 4.1 pyridine is 90% protonated

We must first consider the fundamental difference between basic and non-basic nitrogen. Pyridine contains a basic nitrogen atom and pyrrole contains a non-basic nitrogen atom and we say quite generally that pyridine-like nitrogen atoms are basic and pyrrole-like nitrogen atoms are non-basic. As shown in Scheme 13, when pyridine picks up a proton, the pyridinium ion formed retains the pyridine aromaticity. By contrast, if pyrrole were to be protonated, either on nitrogen or on a ring carbon, the aromaticity would be lost. Because of this, pyrrole does not under normal conditions easily pick up a proton. Analogous to pyrrole, indole is also non-basic. However, the reduced compound indoline is basic. Indoline is not a heteroaromatic compound but is analogous to aniline and of similar basicity.

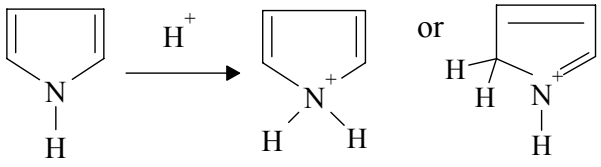
Scheme 13. Pyridine-Like and Pyrrole-Like Nitrogen Atoms

A. Protonation of Pyridine N



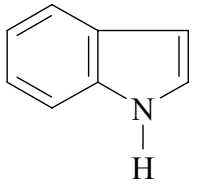
aromaticity retained

B. Protonation of Pyrrole N

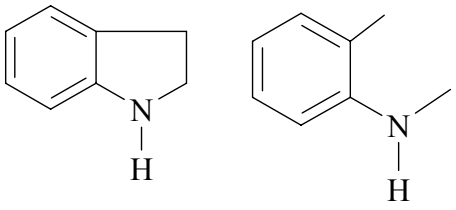


aromaticity lost

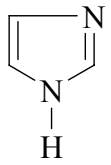
C. Some examples of the different types of nitrogen atoms



non-basic
pyrrole-like N



basic and similar to an aniline
(not heteroaromatic)



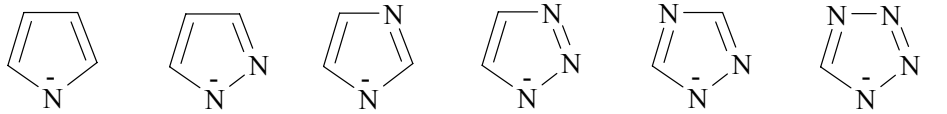
imidazole
one pyridine-like N
one pyrrole-like N

Further information: see Handbook, p. 306.

pKa values of parent nitrogen-containing heteroaromatic rings are shown in Scheme 14. The pyrrole anion is strongly basic: this basicity is reduced by additional pyridine-like nitrogen atoms. Neutral pyrrole has a very low basicity at nitrogen (pK_a = -4) and hence the common description "non-basic nitrogen" (cf. Scheme 28). However, imidazole is quite strongly basic, pyrazole much less so because of the adverse inductive effect. Azoles containing sulfur and especially oxygen have pK_a sharply reduced from their nitrogen analogs, ie. they are much less basic.

Scheme 14. Basicities of Nitrogen in Heteroaromatic Five-Membered Rings (pK_a values)

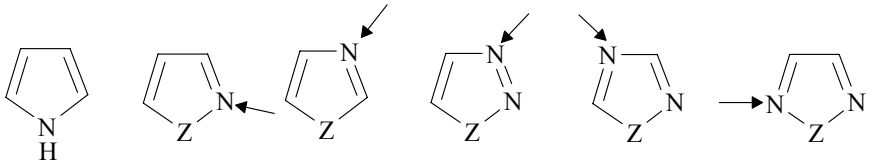
A. Anionic Nitrogen : Azole Anions or Acidity of Neutral Azoles



16.5 14.2 14.4 9.3 10.0 4.9

with increasing number of nitrogen atoms basicity decreases
and acidity of conjugate acid (the neutral azole) increases

B. Neutral Nitrogen: Azoles (Acidity of Azole Cations)



(at N)	Z =	6.9	1.2	2.5	1.2
ca -4	NH 2.5				
	O -3	0.8	-	-	-
	S -0.5	2.5	-	-	-4.9

Note: (i) Pyrrole very weakly basic because no pyridine-like nitrogen

(ii) Imidazole much more basic than pyrazole because of base weakening interaction of adjacent N

(iii) S- and especially O- substitution for NH dramatically reduces basicity

(iv) Additional pyridine-like N atoms also strongly reduce basicity

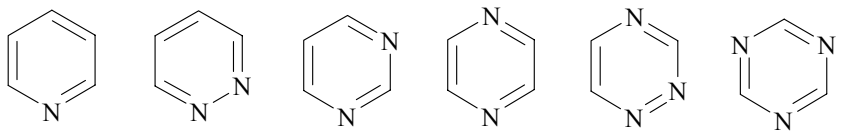
Further information: see Handbook, pp. 379, 377, 177.

The basicity of pyridine is reduced by further pyridine-like nitrogen atoms (Scheme 15): the smaller effect from the ortho- than from the meta- or para- positions is a manifestation of a repulsive lone pair - lone pair interaction in pyridazine, which is relieved in the monocation.

For comparison, the pK_a values of some other common nitrogen compounds are also shown in Scheme 15. Pyrrolidine and piperidine behave as aliphatic amines. Indoline and tetrahydroquinoline behave as substituted anilines.

Scheme 15. Basicities of Six-Membered Heteroaromatics and Non-Heteroaromatics

A. Basicities of Azines (pK_a values)

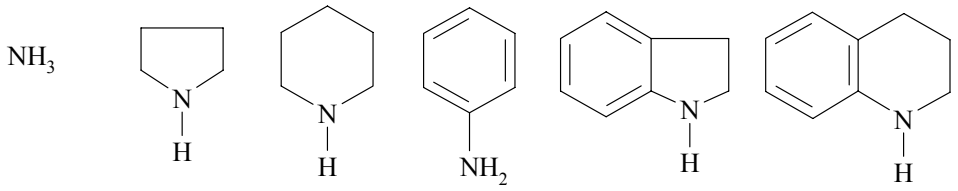


5.1	2.3	1.3	0.6	< 0	< 0
pyridine	pyridazine	pyrimidine	pyrazine	1,2,4-triazine	1,3,5-triazine

Note: (i) Extra N-atoms considerably reduce basicity of pyridine (inductive effect)

(ii) Pyridazine more basic than pyrazine because of the effect of adjacent electron lone pairs (α-effect)

B. Basicities of Some Other Neutral Nitrogen (Non-heteroaromatic) Compounds



9.3	11.3	11.2	4.6	4.9	5.0
ammonia	pyrrolidine	piperidine	aniline	indoline	tetrahydroquinoline

Note: (i) Most aliphatic amines have pK_a around 10 - 11; (ii) Most anilines have pK_a around 4 - 5

Further information: see Handbook, p. 177.

3. The Effect of Substituents: Basicity Values of Substituted Pyridines

The reactivity towards electrophilic attack at a pyridine nitrogen atom is enhanced by electron donor substituents elsewhere in the molecule, particularly at the α- and γ-positions (resonance). Such electronic influences on nitrogen nucleophilicity are conveniently measured by the basicity of substituted pyridines,but steric factors can also influence nucleophility significantly.

The effect of some typical substituents on the basicity of pyridine is shown in Scheme 16. The weakly electron donating methyl group always enhances the basicity and the effect is larger from the 2- or the 4-position than from the 3-position. The effect of t-butyl is very similar to methyl and this shows the small importance of steric hindrance. The much more strongly electron donating amino group also invariably enhances the basicity: the increment is especially large from the 4 position. The 2-amino group, although also directly conjugated also with the nitrogen atom, is less effective because the weak electron accepting inductive effect of the amino group is now significant. In the case of the NHAc and methoxy groups, as compared with the amino group, mesomeric electron donation is weaker and inductive electron withdrawal is stronger. We find that, for these groups, in the 4-position base strengthening results - i.e. the mesomeric donation wins, but in the 2-position by contrast, inductive withdrawal wins and 2-methoxypyridine is a weaker base than pyridine. In the 3-position the effect of NHAc and of OMe on basicity is small.

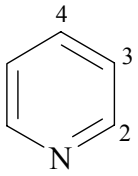
Methylthio is similar to methoxy, but with chlorine we find base weakening at all positions and especially at the 2-position. With a strongly electron acceptor group such as cyano, and especially NO_2, we get a much weaker basicity in all positions, particularly when such substitution occurs in the 2-position. The aldehyde group is considerably less weakening because it exists in aqueous solution in the hydrated form shown in Scheme 16. In the case of the phenyl and vinyl groups, which are weakly electron accepting by inductive effect and plus/minus by the resonance effect: these have little influence but are slightly base weakening from the 2-position and slightly base strengthening at the 4-position. Of considerable importance is the fact that fused benzene rings do not much affect the basicity of pyridine, cf. quinoline, isoquinoline and acridine.

Further information: see Handbook, pp. 178.

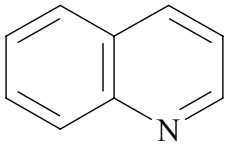
Scheme 16. Effect of Substituents on pK_a of Pyridine

(pK_a of pyridine 5.2, cf. NH_3 9.5)

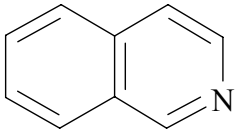
	Me	Bu^t	NH_2	NHAc	OMe	SMe	Cl
2-position	+0.8	+0.6	+1.7	-1.1	-1.9	-1.6	-4.5
3-position	+0.5	+0.7	+0.9	-0.7	-0.3	-0.7	-2.4
4-position	+0.8	+0.8	+4.0	+0.7	+1.4	+0.8	-1.4



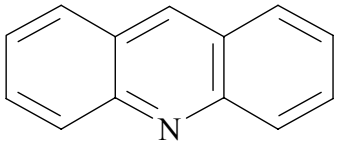
	Ph	$CH_2=CH_2$	CN	NO_2	$CH(OH)_2$
2-position	-0.7	-0.4	-5.5	-7.8	-1.4
3-position	-0.4	-0.4	-3.8	-4.4	-1.4
4-position	+0.3	+0.3	-3.3	-3.6	-0.5



-0.3



-0.1



+0.4

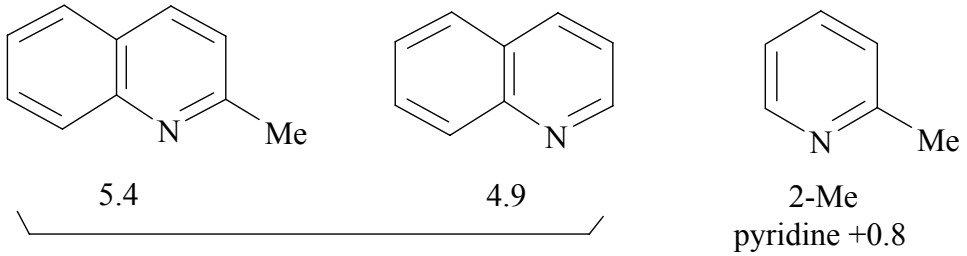
Note: + sign indicates more basic than pyridine
- sign indicates less basic than pyridine

Further information: see Handbook, pp. 178.

The effects of substituents on the pK_a values of other heteroaromatic pyridine-like nitrogen atoms roughly parallels that described above for pyridine. Hence, pK_a values may be estimated using the value for the parent heterocycle and the increment that is derived from the corresponding pyridine. Two examples are shown in Scheme 17; fair agreement is found.

Scheme 17. Approximate Additivity of pK_a Increments

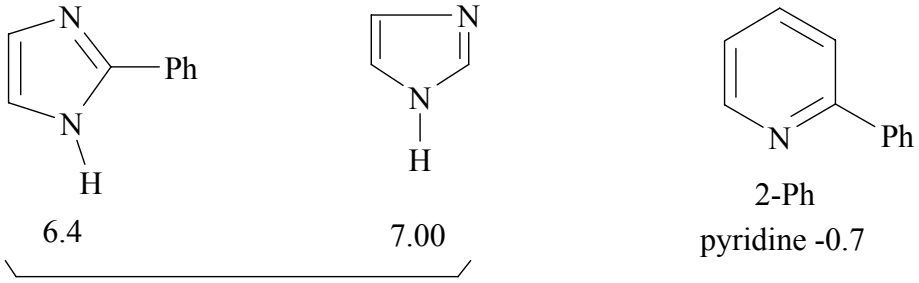
A. Effect of α-methyl group compared in quinoline



5.4 4.9 2-Me pyridine +0.8

difference +0.5

B. Effect of α-phenyl group compared in imidazole



6.4 7.00 2-Ph pyridine -0.7

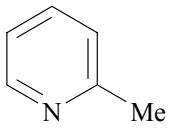
difference -0.6

4. Steric Effects. Reactions with Lewis Acids and Metal Ions

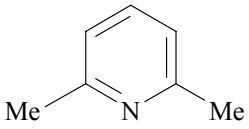
In most reactions of pyridine-like nitrogen atoms with electrophiles (other than with H^+), steric effects are also important for substituents at the 2-position. With t-butyl groups in both the 2- and 6- positions of pyridine even the basicity is affected as is shown in Scheme 18. Scheme 18 also shows the steric effect for α-methyl groups as measured by heats of formation values for BF_3 as electrophile. Steric hindrance is much more important in six-membered than in five-membered rings for the geometrical reason illustrated in Scheme 18.

Scheme 18. Steric Effects of α-Substituents on Reactions of Electrophiles at Ring Nitrogen

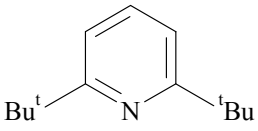
A. On pK_a values: small except in the extreme case of 2,6-di-*t*-butyl where steric hindrance to solvation is found (increment from pyridine is given):



+ 0.8

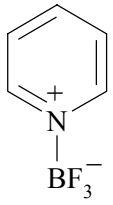


+ 1.4

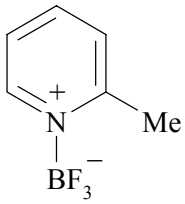


- 1.6

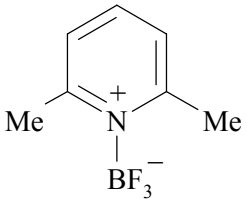
B. For all other electrophiles: much larger as measured by heat of formation (exception: when chelation can occur):



32.9 kcals



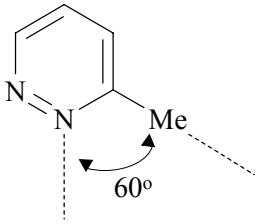
31.2 kcals



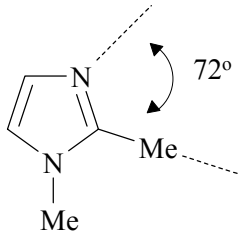
25.4 kcals

C. Dependence on size ring:

very important in 6-rings



less important in 5-rings

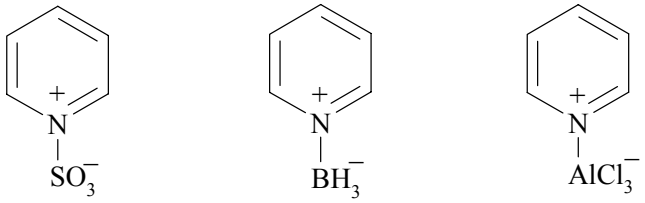


The reaction of pyridines with BF_3, just mentioned, is an example of the formation of a coordination compound with a Lewis acid. Other examples of this general reaction are given in Scheme 19.

Pyridines also coordinate readily with metal ions. Pyridine itself forms a range of tetra- and hexa-coordinated derivatives (Scheme 17). Many chelated complexes are also known, as illustrated in Scheme 19.

Scheme 19. Electrophilic Attack at Ring Nitrogen: Lewis Acids and Metal Ions

A. Lewis Acids give Coordinate Compounds



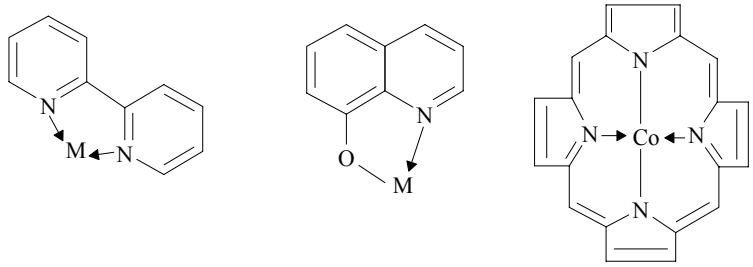
Sulfonating Agent Hydrogenating Agent

B. Metal Ions form Simple Complexes:

e.g. $(heterocycle)_4M$ (planar) and $(heterocycle)_6M$ (octahedral)

where heterocycle = isoxazole, imidazole, triazole, pyridine, etc.

C. Metal Ions form chelated complexes with suitably substituted derivatives:



bipyridyl 8-hydroxyquinoline porphyrin

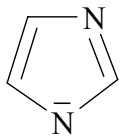
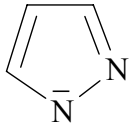
Further information: see Handbook, pp. 179.

5. Reactions with Alkyl and Acyl Halides

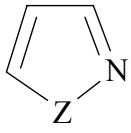
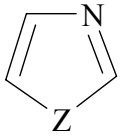
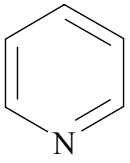
As illustrated in Scheme 20, alkyl halides, tosylates, etc react with a wide variety of nitrogen-containing heteroaromatics. The anions of pyrroles and azoles react particularly readily with alkyl halides to give neutral products, while neutral species react somewhat less readily to afford cations.

Scheme 20. Electrophilic Attack at Ring Nitrogen: Alkyl Halides, Sulfonates, etc.

A. Reactions with anionic species occur very readily:

e.g.  and  with RI,
e.g. in liquid NH_3 or under PTC conditions

B. Reaction with neutral species occur quite readily:

e.g.  and  and  etc.,
with RI, ROTs
at 20^o - 100^o

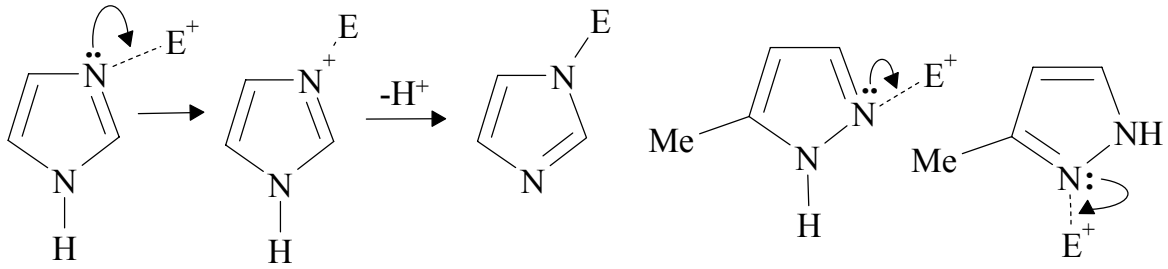
Further information: see Handbook, pp. 383, 180.

In azoles such as imidazole, where (neutral) pyrrole-like and (basic) pyridine-like nitrogen atoms occur in the same molecule, an electrophile always reacts with the pyridine-like nitrogen, see the reaction sequence in Scheme 21. However, reactions can occur in suitable cases via mesomeric anions as also illustrated in Scheme 21.

Scheme 21. Reaction at Cyclic N with Electrophiles Reaction Sequence

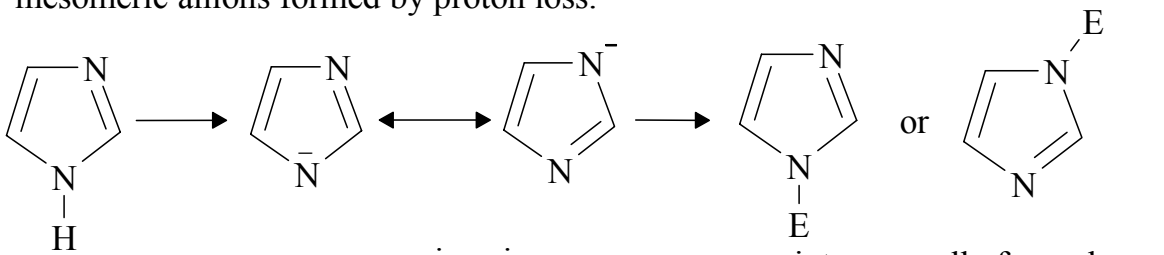
A. Attack on Neutral Molecule

With two annular nitrogen atoms, electrophilic attack occurs at the pyridine-like (multiply bonded) nitrogen.



B. Reaction with Electrophile in presence of base

Electrophilic reagents can also attack at either one of the ring nitrogen atoms in the mesomeric anions formed by proton loss.



mesomeric anion - nitrogen atoms equivalent

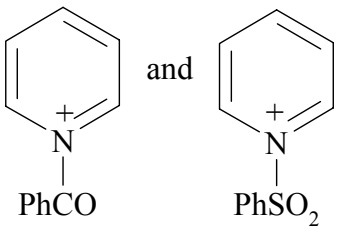
mixture usually formed if unsymmetrically substituted

Further information: see Handbook, p.376.

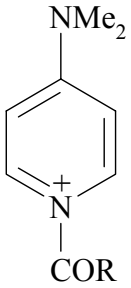
Acyl halides react with pyridines to give intermediates, which are not normally isolable (Scheme 22). 4-Dialkylaminopyridines are very good catalysts for the acylation of even very unreactive alcohols. With acylating agents the catalysts form, even in non-polar solvents, high concentrations of N-acylpyridinium salts which are present as loosely bound, highly reactive ion pairs. N-Acylpyrroles can be isolated but are easily hydrolysed back to pyrrole. N-Acylazoles are good acylating agents.

Scheme 22. Electrophilic Attack at Ring Nitrogen: Acyl Halides

A. Pyridines form unstable addition products which are strong acylating agents

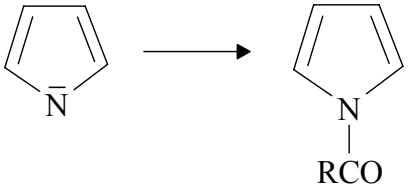


intermediates for benzoylation, sulfonation



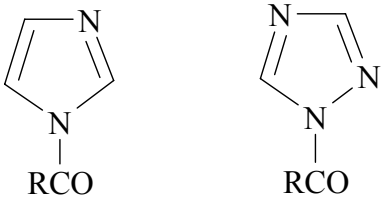
more stable particularly good catalyst

B. Pyrrole Anions form acyl derivatives



easily hydrolyzed

C. NH-Azoles form acyl derivatives



acylating agents

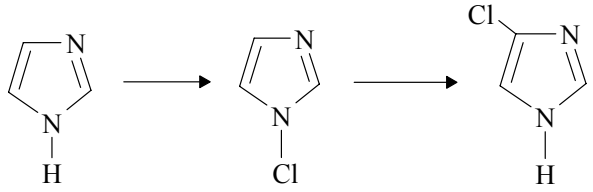
Further information: see Handbook, pp. 385, 181.

6. Reactions with Halogens

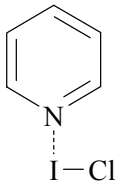
Halogens react readily with anionic nitrogen to give N-halogeno derivatives which often rearrange readily, e.g. in the imidazole and 2-pyridone series (Scheme 23). With neutral pyridine-like nitrogen, weak complexes are formed with halogens.

Scheme 23. Reaction of Halogens at Ring Nitrogen and Subsequent Rearrangement

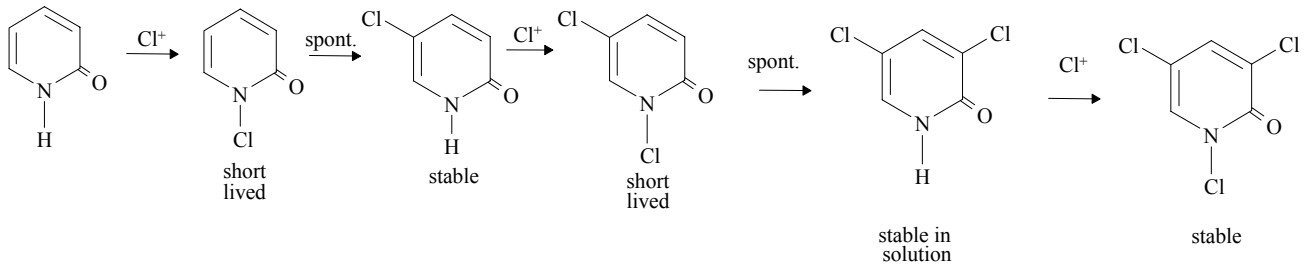
A. Imidazole forms N- then C-chloro derivatives



B. Pyridine forms a weak complex



C. 2-Pyridone forms successively N- then C-substitution products



Further information: see Handbook, pp. 386, 182.

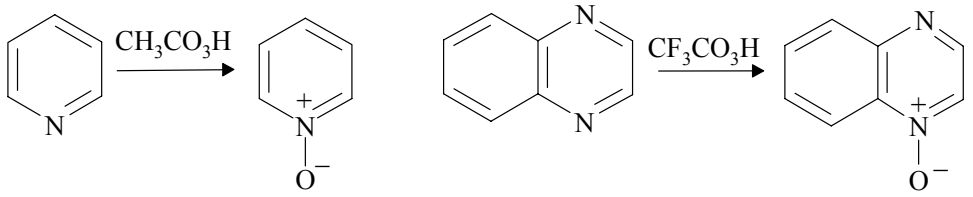
7. N-Oxidation and N-Amination

This reaction is illustrated in Scheme 24 for six-membered rings. It is rather general and subject to the usual electronic and steric influences. Some examples of N-oxide formation from azoles are known (Scheme 24), but frequently the reaction yields other products. Thus nucleophilic attack of a peroxide anion on the azolium cation often gives ring-cleaved derivatives.

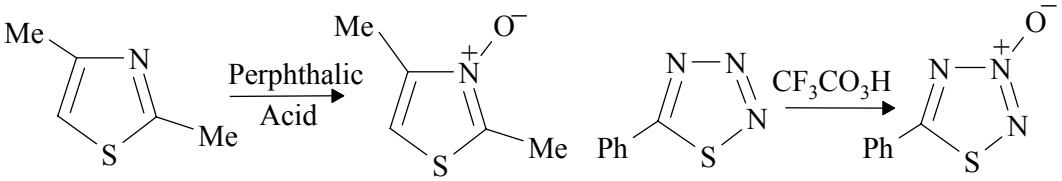
Pyridines can be N-aminated to form N-aminopyridinium cations by NH_2Cl, NH_2OSO_3- and other electrophilic aminating agents. Sulfonyl azides yield sulfonyl-N-amides (Scheme 24). With hydroxylamino-O-sulfonic acid, N-unsubstituted azole anions often give N-amino products (Scheme 24).

Scheme 24. Electrophilic Attack at Nitrogen N-Oxide and N-Imide Formation

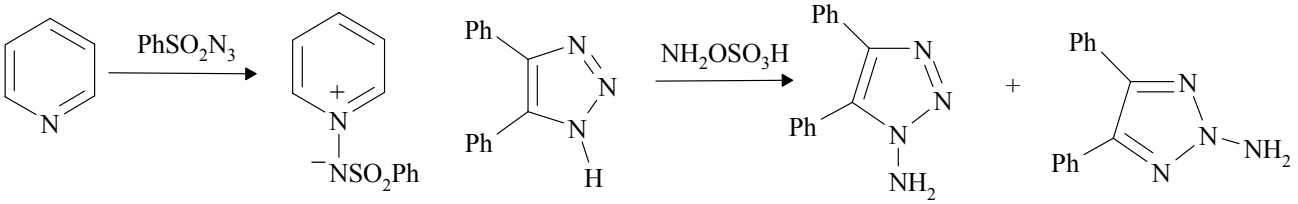
A. Pyridines react very readily with peracids, azines less so:



B. Examples of N-Oxide Formation by Azoles



C. Examples of N-Imide and N-Amide Formation



Further information: see Handbook, pp. 386, 183, 184.

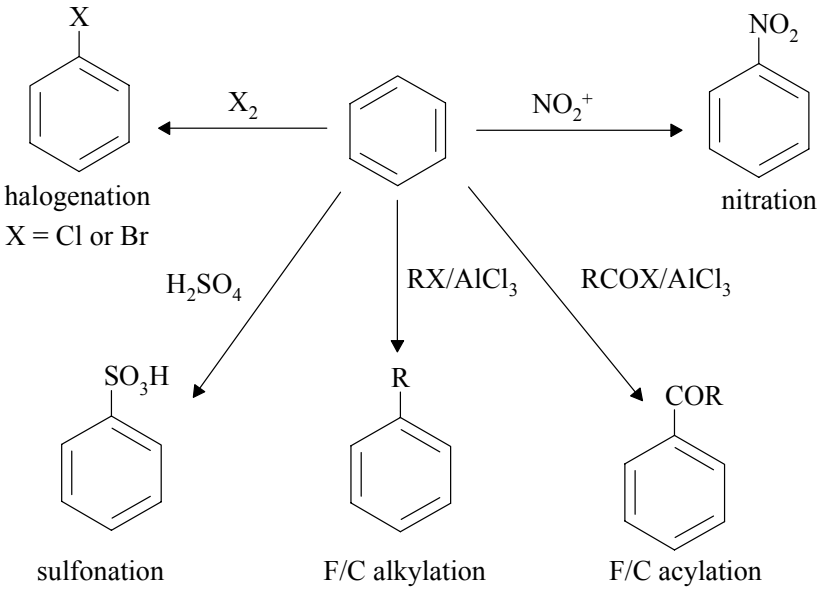
IV. ELECTROPHILIC ATTACK AT RING CARBON ATOMS

1. Ease and Nature of Reaction

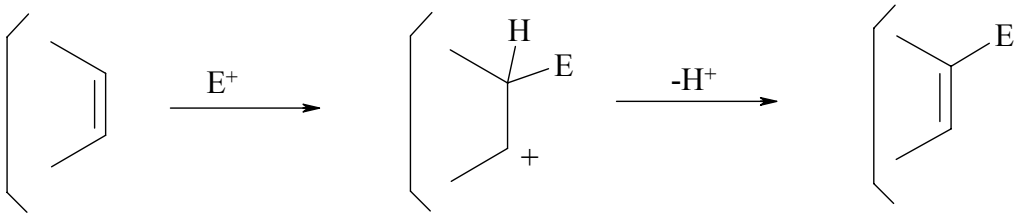
Electrophilic substitution is the archetypal reaction of benzene and its derivatives. The most important examples of these electrophilic substitutions are shown in Scheme 25. The effect of substituents on the rates of electrophilic substitution reactions is very significant.

Scheme 25. Electrophilic Substitutions of Benzene

A. The five most important electrophilic substitutions



B. The Mechanism of Electrophilic Substitution in Benzene

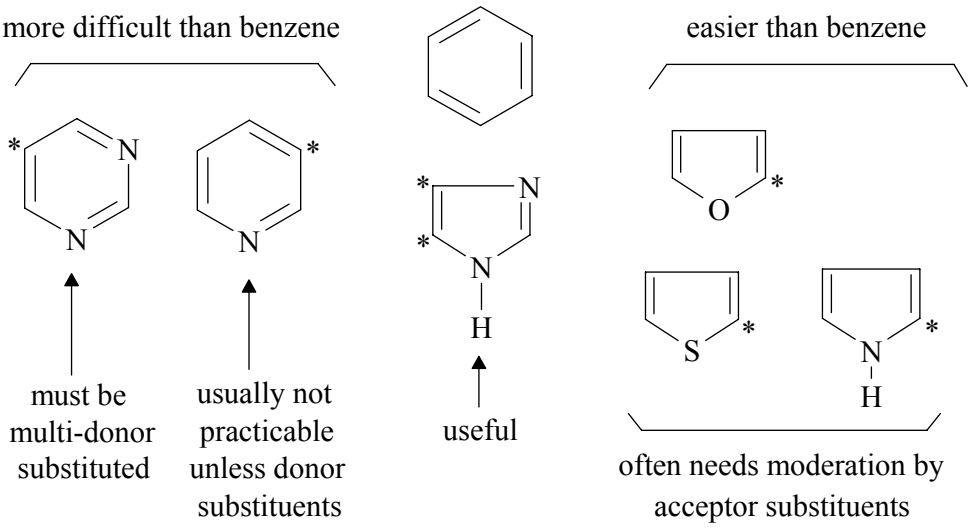


Pyridine-like and pyrrole-like nitrogen atoms are quite different in their influence on electrophilic substitution reactions. Pyridine-like nitrogen atoms slow down electrophilic substitution just like a strongly meta-directing substituent does in benzene, whereas a pyrrole-like atom accelerates electrophilic substitution just as a strongly-activating and ortho / para-directing substituent does in benzene.

The ease of electrophilic substitution on the parent heterocyclic rings, and the utility of such reactions is compared in Scheme 26 with those for benzene. Positions of predominant substitution are noted with asterisks. Characteristics of such reactions are also noted.

Scheme 26. Electrophilic Substitution: Effect of Heteroatoms

A. Feasibility of Electrophilic Substitution in different types of Heteroaromatics



B. Directive effects of C-substituents as in benzenoid chemistry:

(i) NH_2, OH - strong donor (o/p) : large increase in reactivity

(ii) alkyl, subst-alkyl - weak donor (o/p) : increased reactivity

(iii) halogen, SR - donor/acceptor (o/p) : decreased reactivity

(iv) NO_2, COR, SO_2R - acceptor (m) : large decrease in reactivity

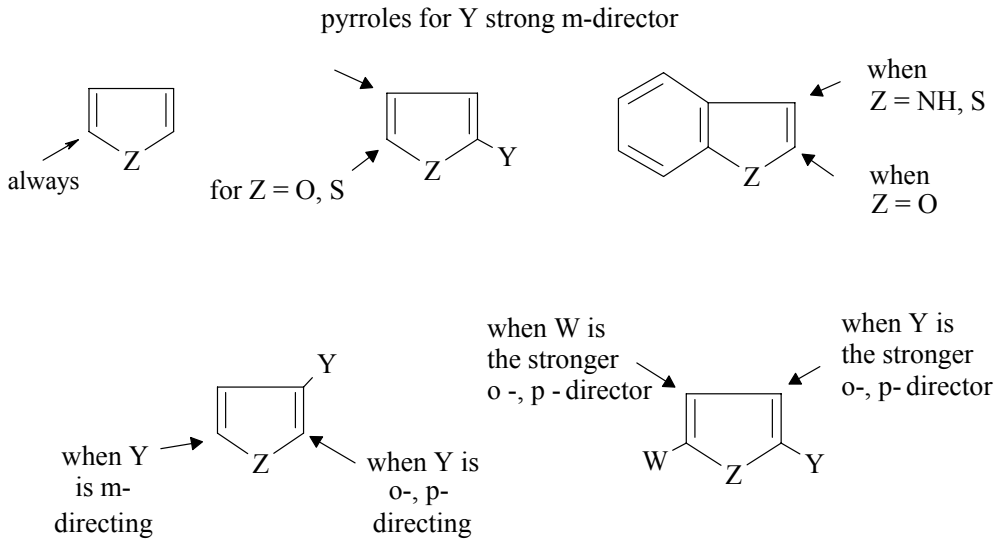
Further information: see Handbook, pp. 388, 185.

2. Five-membered Rings with One Hetero Atom: Neutral Compounds

The five-membered heteroaromatic rings with one heteroatom undergo easy electrophilic substitution cf. Scheme 27. The orientation is nearly always α i.e. at the 2-position.

Scheme 27. Electrophilic Substitution of 5-Membered Rings with one Hetero Atom: Pyrroles, Thiophenes and Furans

A. Orientation:



B. Ease of reaction: Much easier than benzene, thiophene about equals mesitylene; furan and pyrrole comparable to phenol

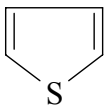
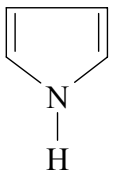
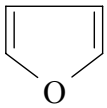
C. Effect of Substituents: one meta directing group makes the reaction more difficult than benzene; two meta directing make it very difficult

Further information: see Handbook, pp. 302-304.

Scheme 28 summarizes the reaction conditions needed for typical electrophilic substitution reactions of thiophene, pyrrole and furan. In thiophene and furan the tendency for substitution to occur at a free α-position overcomes other substituents directive influence.

Even in the pyrrole nucleus, the directive effects of substituents are weakened by the overwhelming tendency for electrophilic substitution reactions to go in the α-position. Thus mixtures of 4-and 5-substitution products are formed on electrophilic substitution of, for example, pyrrole-2-carboxylic esters and aldehydes.

Scheme 28. Electrophilic Substitution of Thiophene, Pyrrole, Furan: Conditions / Yields

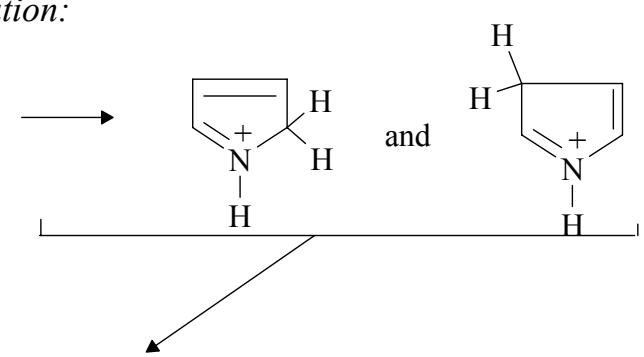
	Thiophene 	Pyrrole 	Furan 
nitration	HNO_3-HOAc good yield	HNO_3-Ac_2O poor yield	HNO_3-Ac_2O gives addition product
sulfonation	H_2SO_4, -20° good yield	Pyridine-SO_3 fair yield	Pyridine-SO_3 fair yield
halogenation	easy; mono, di, tetra isolated	only tetra derivatives	usually all decomposed
acylation	F/C with $SnCl_4$	Ac_2O, no catalyst	Ac_2O, no catalyst
chloromethylation	goes well	difficult	goes well

Further information: see Handbook, pp. 307-314.

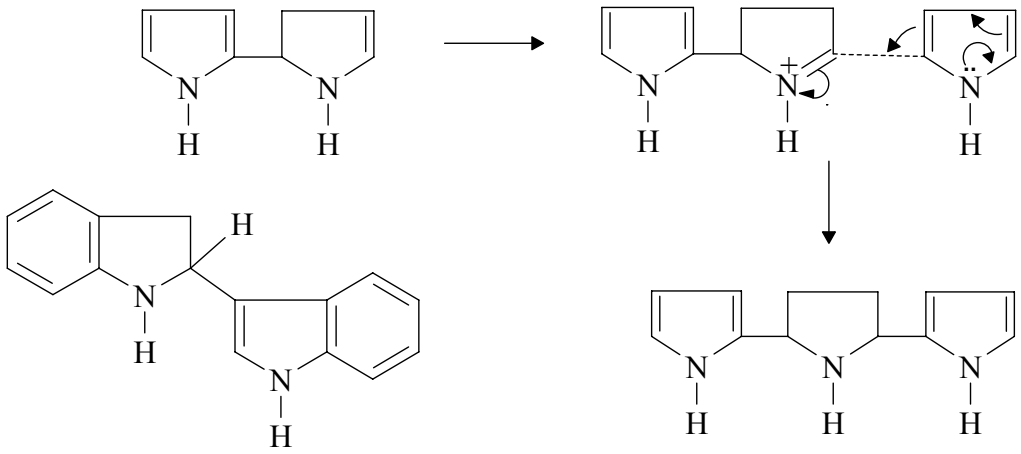
Pyrroles do not form cations by proton addition at the nitrogen, instead with strong acids proton addition takes place at a carbon atom. Such cations can undergo further reactions, for example, oligomerization, or polymerization as shown in Scheme 29.

Scheme 29. Reactions of Pyrrole with Acids

A. Cation formation:



B. Polymerization:



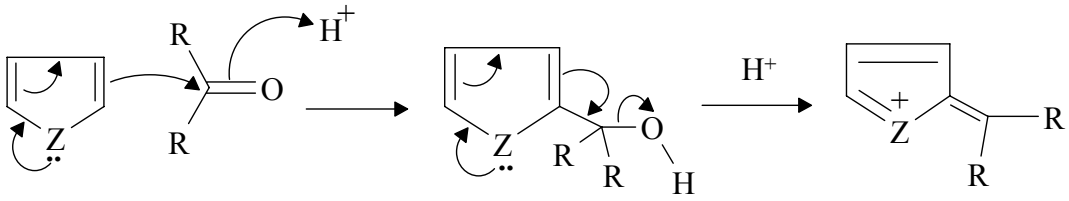
from indole

Further information: see Handbook, pp. 321.

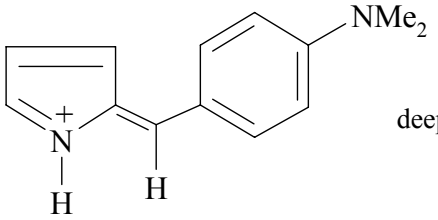
The five-membered heteroaromatic rings with one heteroatom also react quite readily with various types of carbonyl containing compounds. Some examples of this are shown in Scheme 30. The initially-formed hydroxyalkyl compound can form a stable cation (as in the Ehrlich test) or react with more heterocycle to give di- or tetra-meric products.

Scheme 30. Reaction with Carbonyl Compounds

A. Initial Reaction:

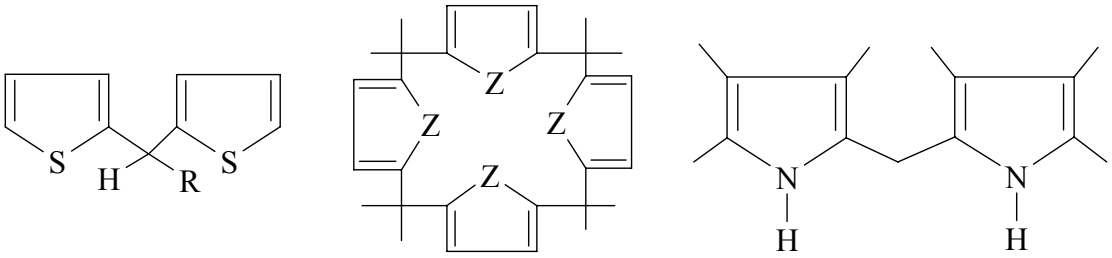


B. Carbonium ion stable: Ehrlich test for Pyrroles and Indoles



deep red/violet color

C. Reaction with more heterocycles to give



Further information: see Handbook, pp. 314-315.

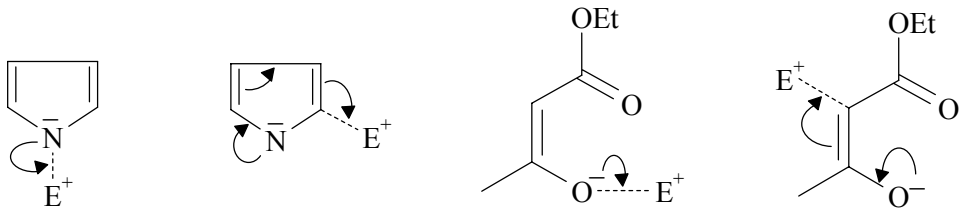
3. Five-membered Rings with One Hetero Atom: Pyrrole Anions

The pyrrole anion reacts still more readily, even with weak electrophilic reagents. Now reaction can take place either at a carbon or at the nitrogen atom. Mixtures of products are often formed: see Scheme 31, and note the analogy to the ambident anion of acetoacetic ester.

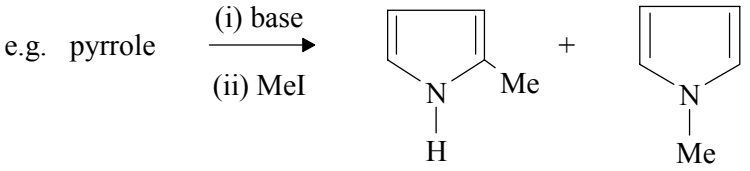
Reactions are conducted either by complete formation of the anion using a strong base, or by formation of an equilibrium proportion of anion using a weaker base. The latter procedure can only be used when the base does not react irreversibly with the electrophile subsequently added. A close analogy exists here to reactions of ketones with electrophiles, which can also involve complete or partial anion formation, cf. acetone alkylation with NaH, bromination with NaOH.

Scheme 31. Enhanced Reactions of Pyrrole Anions with Electrophiles

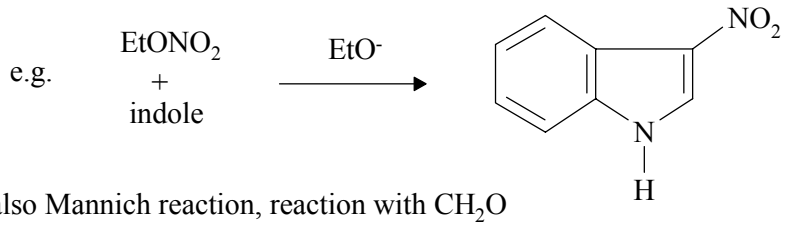
A. Heterocycle ambident anion: cf. acetoacetate ambident anion



B. Complete anion formation by strong bases e.g. MeMgBr or $NaNH_2$ for reactions with CO_2, RBr, RCOCl (Mixed 1- and 2- substituted)



C. Partial formation of anion with EtONa, NaOH (weaker bases) for reactions where no irreversible reaction between base and electrophile



also Mannich reaction, reaction with CH_2O

Further information: see Handbook, pp. 312.

4. Six-membered Rings: Pyridines, etc.

The pattern of reactivity of six-membered rings with one heteroatom with electrophiles is shown in Scheme 32 for pyridines. There is always the choice of attack at a carbon atom or the heteroatom, but generally reaction at the heteroatom (especially if nitrogen or oxygen) is easy and reversible whereas attack at the carbon atom is more difficult and less reversible.

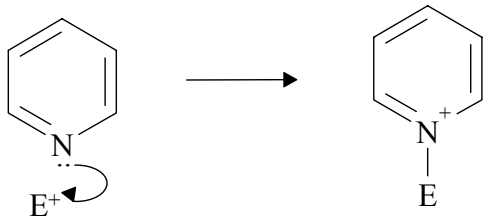
Scheme 32. Pyridine-Reactions with Electrophiles at N- and C- Atoms

A. Reaction at N

Easy and Reversible

H^+, Lewis Acids, Metal Ions,

RX, Halogens, Peracids



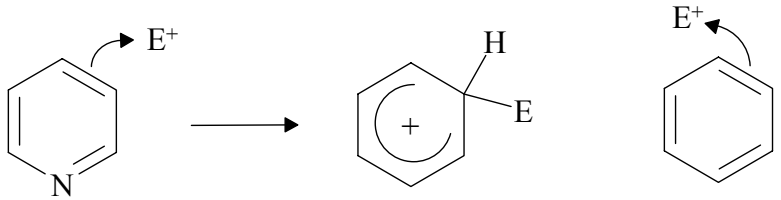
Compare: $R_3N:E^+$

B. Reaction at C

Difficult and Irreversible

(Because of Unreactive Cation)

H^+, NO_2^+, SO_3, RCO^+, R^+, Ozone



Compare:

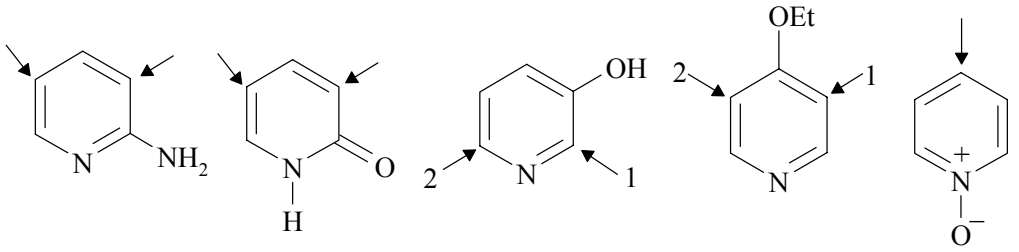
Electrophilic attack on a carbon atom of pyridine is difficult, however one strongly donating substituent such as amino or methoxy cancels out the effect of the pyridine nitrogen to a first approximation. Orientation in some common compounds is shown in Scheme 33.

Scheme 33. Electrophilic Attack on Ring Carbon in Substituted Pyridines

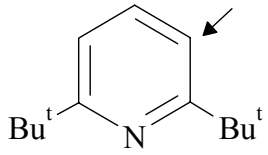
A. Nitration: Pyridine at 300° / H_2SO_4, SO_3, HNO_3

Lutidine & collidine easier, better yields

all following comparatively readily / good yields:



B. Sulfonation: Orientation & conditions similar to those for nitration



2,6-di-*t*-butyl pyridine is an exception:
it reacts with SO_3 / SO_2 at 0 °C because the
large electrophile cannot react at the N - atom

C. Halogenation: Vapor phase 3,5-orientation with pyridine;
activated derivatives undergo easy halogenation

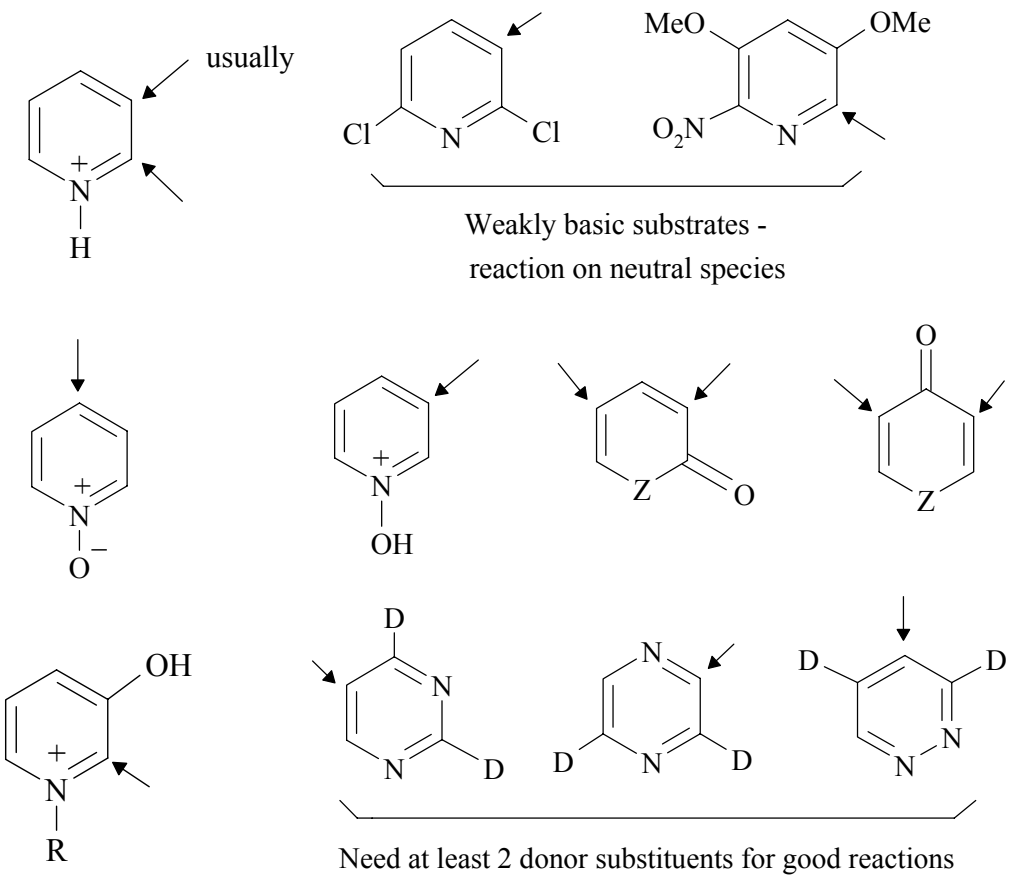
D. Nitrosation, Diazocoupling, Mannich reaction : by compounds with OH or NH_2

Further information: see Handbook, pp. 185.

Electrophilic substitution at pyridine carbon atoms usually takes place on the cationic species in the 3-position (Scheme 34). However, orientation can be directed into other positions by sufficiently strongly directing substituents: e.g. into the 2-position in 3,5-dimethoxypyridine. If the basicity of the pyridine nitrogen atom is reduced by electron withdrawing groups then reaction can take place on the free base species, e.g. 2,6-dichloropyridine. Pyridones are substituted in the 3,5-positions: 3-hydroxypyridine at the 2-position; pyridine N-oxide at the 4-position. Electrophilic substitution into the azines needs at least two strong donor substituents to be effective (cf. Scheme 34).

Halogenation of pyridines is rather easier than corresponding nitration or sulfonation because halogenation can take place in the vapor phase, where the stability of the complex formed by halogen attack at the pyridine nitrogen atom is low and thus there is ample free base available.

Scheme 34. Orientations of Electrophilic Attack in Substituted Pyridines and Azines

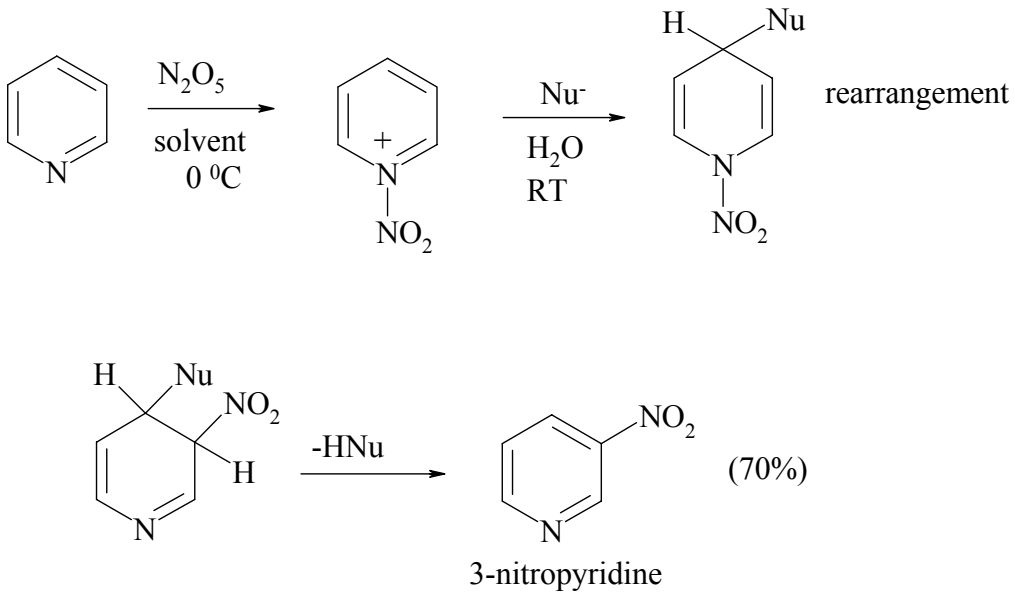


Further information: see Handbook, pp. 186, 189.

5. Bakke Nitration

A recent, elegant way to overcome the resistance of pyridine to nitration at carbon has been described by Bakke. Pyridine (for example) is converted into the N-nitropyridinium cation, which is then subjected to very ready nucleophilic attack, at the 4-position, to give a dihydropyridine which rearranges spontaneously to the 3-nitro isomer, which finally aromatises by elimination of H-Nu. The nitrating agent is N_2O_5 or $NO_2^+BF_4^-$, originally in liq.SO_2, but this can be conveniently replaced by an organic solvent (CH_3NO_2, CH_3CN, THF) containing two moles of SO_2 per mole of pyridine (see Scheme 35). Bisulfite is the best nucleophile, adding rapidly and being readily eliminated. The N-NO_2 pyridine species must be formed first, before adding the nucleophile, The rearrangement of NO_2 from N to C is intramolecular or via a tight ionpair. Substituted (but unactivated) pyridines also nitrate in good yield, and much wider application of this reaction sequence is to be expected.

Scheme 35. Bakke Nitration of Pyridine



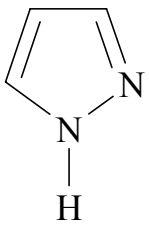
6. Azoles

The pattern of electrophilic substitution (Scheme 36) and some typical conditions required (Scheme 37) are given in the following schemes.

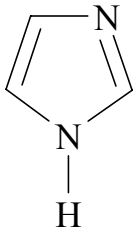
Scheme 36. Electrophilic Substitution in Azoles

A. The total effect of the several heteroatoms in one ring approximates the superposition of their separate effects. Pyrazole, imidazole, oxazole, and isoxazole undergo nitration and sulfonation about as readily as benzene; thiazole and isothiazole react much less readily, and oxadiazoles, thiadiazoles, triazoles, etc. with still more difficulty. In each case halogenation is easier than the corresponding nitration or sulfonation.

B. Pyrazole and imidazole anions react with electrophilic reagents about as readily as phenol, undergoing diazo coupling, nitrosation, and Mannich reactions; cf. the increased reactivity of pyrrole anions over the neutral pyrrole species.



Pyrazole



Imidazole

Further information: see Handbook, pp. 388-395.

Scheme 37. Experimental Data for Nitration and Sulfonation of Azoles

Compound	Position Substituted	Reaction Conditions: Sulfonation	Reaction Conditions: Nitration
Pyrazole	4	H_2SO_4 - SO_3 , 100°	HNO_3 - H_2SO_4 , 100°
Imidazole	4 (=5)	H_2SO_4 - SO_3 , 160°	Boiling H_2SO_4 - HNO_3
3-Methylisoxazole	4	HSO_3Cl , 100°	HNO_3 - H_2SO_4 - SO_3 , 70°
Isothiazole	4	H_2SO_4 - SO_3 , 150°	HNO_3 - H_2SO_4 , 230°
Thiazole	5	H_2SO_4 - SO_3 - Hg , 250°	
4-Methylthiazole	5	H_2SO_4 - SO_3 , 200°	HNO_3 - H_2SO_4 - SO_3 , 160°
2,5-Dimethylthiazole	4	H_2SO_4 - SO_3 , 200°	HNO_3 - H_2SO_4 - SO_3 , 160°